LETTERS

Effects of high-fat diet-induced gut microbiota dysbiosis: far beyond the gut

We read with great interest the attractive study by Ding N *et al*,[1] which reported that the dysbiosis of gut microbiota induced by high-fat diet (HFD) was one of the primary causes for the impaired sperm production and motility. It is likely mediated by elevated blood endotoxin, epididymal inflammation and the dysregulation of testicular gene expressions. We commend the authors for such a rigorous work on this critical issue. We would like to raise several concerns about this study.

According to the data in this study, metagenomic sequencing may be needed to further explore the mechanisms by which certain key bacteria disrupt spermatogenesis and sperm motility. Moreover, whether probiotics supplementation can modulate gut microbiota and improve spermatogenesis and sperm motility are also worthy of exploration.

Faecal microbiota transplantation (FMT) was performed in this study. To be specific, a gnotobiotic mouse experiment may better dissect the mechanism of how the dysbiosis-induced by HFD impair the spermatogenesis. As most studies did,[2–4] gnotobiotic mouse model may avoid the side effect of the antibiotics and the interference from the indigenous microbiota, which will, in turn, affect the final outcome of the study.

Another question is about HFD. The composition of HFD is very complicated, such as the different proportions of saturated fat, protein[5] and heme,[6] which may cause a large difference in the gut microbiota. Thus which ingredients or the metabolites in HFD and how they cause gut microbiota dysbiosis to damage spermatogenesis and sperm motility remain unknown. Lately our group investigated the relationship between gut dysbiosis induced by the metabolites of HFD and colorectal cancer.[7] HFD could increase the secretion of primary bile acids which have been reported to play a role on fertility troubles and could participate to damage spermatogenesis.[8] The primary bile acids were then transformed by the intestinal bacteria into secondary bile acids. Meanwhile, secondary bile acid has been shown to alter the composition of gut microbiota.[7 9] Therefore, there is indeed an interaction between bile acids and gut microbiota. It deserves further study whether the crosstalk between bile acids and microbiota is responsible for the damaged spermatogenesis and sperm motility after HFD intake.

In the original article, HFD-induced dysbiosis has been shown to damage sperm production and motility by multiple ways. It will be interesting to know the key factor and how it damages spermatogenesis and sperm motility for the further study. For instance, it has been reported that semen has a unique microbiome which could originate from gut. Some microorganisms were associated with sperm abnormalities, especially with aberrant motility, deficient mitochondrial function and loss of DNA integrity.[10] Therefore, whether there is an increase in certain pathogenic bacteria or a decrease in certain probiotics after HFD intake to disrupt testicular mitochondrial functions may attract readers' attention.

At last, in the clinical part, it may be interesting for readers to know the comprehensive information of the participants, such as the dietary patterns, alcohol intake, smoking and Body Mass Index (BMI), etc. Since this study focuses on the effects of HFD-induced dysbiosis on spermatogenesis and sperm motility, it may also be necessary to ask participants about their dietary intake to achieve consistency with animal experiments. Moreover, multiple factors have been reported to affect sperm motility. For example, increased BMI had negative correlations with ejaculate volume, sperm concentration, motility and morphology.[10] Therefore, if these factors are not included, it may not be able to accurately prove that the decline of sperm concentration or motility is due to the HFD-induced gut dysbiosis.

In summary, this study represents a critical contribution to infertility. More in-depth research may be required to clarify the potential mechanisms.

Tianyu Liu, Bangmao Wang, Hailong Cao

Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Tianjin Institute of Digestive Diseases, Tianjin Key Laboratory of Digestive Diseases, Tianjin, China

Correspondence to Dr Hailong Cao, Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Tianjin Institute of Digestive Diseases, Tianjin Key Laboratory of Digestive Diseases, 300052 Tianjin, China; caohailong@tmu.edu.cnDr Bangmao Wang; mwang02@tmu.edu.cn

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ORCID iD
Hailong Cao http://orcid.org/0000-0002-0147-7826

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